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EPIDEMIOLOGY AND EPIZOOTIOLOGICAL INVESTIGATIONS OF  
HEMORRHAGIC FEVER VIRUSES IN THE CENTRAL AFRICAN  
REPUBLIC

Final Report

A. J. Georges and J. L. Durosoir

December 14, 1985

Supported by:

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Institut Pasteur  
28 Rue du Docteur Roux  
5724 Paris, Cedex 15, France

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A.J. GEORGES and J.L. DUROSOIR

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)  EBOLA, MARBURG, CONGO-CRIMEAN-HEMORRHAGIC-FEVER, AND RIFT VALLEY FEVER-VIRUS SEEM TO BE ENDEMIC IN THE C.A.R. IN 1984 USAMRIID AND PASTEUR INSTITUTE IN PARIS SET UP A COLLABORATIVE PROGRAM OF RESEARCH WITH INVOLVEMENT OF THE PASTEUR INSTITUTE OF BANGUI LOCATED IN A COUNTRY WHERE ANTIBODIES PREVALENCE RATES AGAINST THESE VIRUSES ARE VERY HIGH. OUT OF 1398 HUMAN SERA COLLECTED OVERALL THE COUNTRY, WE WERE ABLE TO SHOW QUITE A LOW PREVALENCE FOR RVF, CCHF, AND ARENAVIRUSES, AS COMPARED TO A HIGH ONE FOR FILOVIRIDAE. LONG TERM EPIDEMIOLOGICAL STUDIES ARE NEEDED.		

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### SUMMARY

Based upon preliminary surveys and/or virus isolations, Ebola, Marburg, Congo-Crimen, haemorrhagic fever and Rift-Valley-Fever virus seem to be endemic in the Central African Republic (CAR). The occurrence of these agents poses risk to both the local population, and to travelers or foreigners living in the CAR, who could carry these pathogens out of the country, and infect residents of other parts of the world.

In 1984 US AMRIID and PASTEUR INSTITUTE in PARIS decided to set up a cooperative program of research on Viral haemorrhagic Fevers (VHF), in the CAR. INSTITUTE PASTEUR of BANGUI (IPB) was asked to develop field research and to collect human specimen from numerous villages in an attempt to define the prevalence and distribution of haemorrhagic fever infections in different ecological zones of the country.

Human antibody prevalence rate of VHF has been determined in several areas. A total of 1398 human sera has been obtained. Patients were from the following districts: BANGASSOU (and HAUT MBOMOU): 222; BAMBARI (and OMBELLA MPOKO including BANGUI town): 194; BERBERATI and NOLA area (SANGHA): 292; NDELE area (VAKAGA district): 307; BOSSANGOA (and NANA MAMBERE plus OUHAM PENDE): 383.

Serum samples have been aliquoted, one portion stored at PASTEUR INSTITUTE in BANGUI (IPB) for routine analysis by immunofluorescence assay, and the remaining portion sent to USAMRIID for control and additional analysis by alternative methods.

The sero survey showed a low antibody prevalence against RVF virus, CHF-Congo, and Arenavirus, while interesting data were obtained for FILOVIRIDAE. The sero prevalence for both EBOLA and MARBURG was very high, specially in the NORTHERN DISTRICTS and in the eastern part of the CAR.

These preliminary results document the presence in CAR of virus causing haemorrhagic fevers in other countries of Central Africa, and allow selection of areas for potential long term ecological and epidemiological studies.

Nevertheless these data, remain incomplete at this point, and there is a particular need to continue researchs. The INSTITUTE PASTEUR is most interested in pursuing this continued research in collaboration with USAMRIID.

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## FOREWORD

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Since 1979, the IPB research program has concentrated on arbovirus haemorrhagic fever and diarrhoeal diseases. Studies of febrile patients allowed us to identify an infecting arbovirus in about 8% of the patient studies.

In 1980, using FA assay, we started a program of sero surveys of haemorrhagic fevers in the whole country : 2672 human sera have been screened. Based upon these preliminary data and limited virus isolations we were able to show that five hazardous haemorrhagic fever viruses : Ebola, Marburg, Lassa, Congo-Crimean and Rift-Valley-Fever, were endemic in the Central African Republic. These initial successful sero surveys were found interesting by both US AMRIID and IPB and we decided to set up a common research project.

The specific aims of the project were to develop a cooperative program to :

- 1) evaluate aims of the potential threat of viral haemorrhagic fever infections in the country by determining antibody prevalence rate in human and animals in several ecological zones.
- 2) establish preliminary ecological studies to implicate vertebrates as reservoir and/or vectors, by correlating the antibody prevalence rate in wild peridomestic animals with that in humans.
- 3) locate areas for indepth field studies to determine the incidence of subclinical and clinical infections and environmental factors which could influence the maintenance and dissemination of these agents.
- 4) evaluate existing serological methods and those currently under developpment such as ELISA or WESTERN BLOTT to establish and control valid fieldable serological assays for the agents.

The initial INSTITUT PASTEUR-US AMRIID haemorrhagic fever virus sero survey was highly succesful.

It confirmed the Institute's original observations, turned up several interesting and unexpected findings, and established a starting point for more comprehensive and extended studies. Among the six zones we explored, the findings suggest that the VAKAGA district in the North may provide the best opportunity to study the epidemiology of FILOVIRIDAE.

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## LIST OF APPENDIXES

1 - Scientific publications:

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## REPORT

=====

Between October 1984 and July 1985, we were able to collect 1398 human sera from 6 districts of the CAR. All the specimens were screened double blind at 1/16 dilution on CRELM slides and the positive tited on monovalent antigen spots. This screening has been performed in BANGUI as well as in FREDERICK. The IFA data on CCHF, Rift and Lassa are unimpressive, while data concerning Filoviridae are really very interesting.

Methods :

Five different areas have been studied :

1 : BANGASSOU and villages around this main town located in the district of HAUT MBOMOU. 222 samples were collected. In this area, in 1979 we observed 2 persons with fluorescent MARBURG antibodies ( 1 ).

2 : BAMBARI and OMBELLA MPOKO district including BANGUI, capital of the country : 194 patients were sampled.

3 : BERBERATI and NOLA area (SANGHA) : 292 patients bled.

4 : BOSSANGO and NANA MANBERE : 293 sera collected.

5 : VAKAGA district : 307 people studied.

In each village 5 to 10 houses, were selected. All individuals between 10 and 50 years of age were identified and sampled. Lists of persons with family name, first name, and approximate age, have been established for further vertical studies.

In 1985 a second trip only in the VAKAGA district allowed us to check some patients. In some areas wild peridomestic and domestic animals have been bled and some of the rodents organs have been treated for viral isolation. Serum samples have been aliquoted and sent to USAMRIID in liquid nitrogen as previously asked in the contract.

Results:

Between 9% and 37% of the whole population are positive for 1 or more of the viral antigen. In fact the prevalence of antibodies is different whether we consider each family of virus.

BUNYAVIRIDAE AND PHLEBOVIRUS (RVF):

Up to now, serosurveys have shown a low prevalence of the : virus : 0.4% for the whole country. Nevertheless in several areas antibody prevalence rates demonstrate RVF virus circulation. Sera found to be positive for FA, have been controlled using neutralisation.

Complete results are given in table 1:

Table 1 :  
Rift-Valley-fever virus serosurvey :

DATE OF SAMPLING	ORIGIN	TOTAL	POS	% POS
JUN 84	PAQUA	96	0	0
JUN 84	BANGUI	101	1	1
JAN 85	BALEMBE	31	0	0
JAN 85	BOUAR	112	2	1.8%
JAN 85	DIKA	75	0	0
JAN 85	DONGO BODAMA	59	0	0
JAN 85	NDONGUE	10	0	0
FEB 85	ZEMIO	140	0	0
FEB 85	BAMBOUTI	82	0	0
TOTAL		706	3	0.4%

In 1984, we isolated 3 new Rift-Valley-fever virus strains in CAR.

2) Nairoviruses : CHF Congo virus.

The sero survey has shown a low prevalence of the CHF Congo virus in the CAR : 1.7% .

The complete results are given in table 2. We must note that all the positive sera were from the same area in the North-West of the CAR, including two important towns : Bouar and Boguila.

Table 2:  
CCHF virus serosurvey :

Date of Samples	Geographical origin	N° Tested	N° Pos	% Positive
June 1984	PAQUA	96	1	1
June 1984	BANGUI	101	0	0
January 1985	BALEMBE	31	0	0
January 1985	BOUAR	112	4	3.6
January 1985	DIKA	75	4	5.3
January 1985	DONGO BODAMA	59	3	5.1
January 1985	NDONGUE	10	0	0
February 1985	ZEMIO	140	0	0
February 1985	BAMBOUTI	82	0	0

One strain of CCHF virus was isolated from a wild rodent Mastomys sp, caught in the North-West of the CAR, near the town of Boheng.

-3) Arenaviridae :

All the surveys have shown a very low prevalence for Lassa virus antibodies (0.8%). The complete results are given in table 3.

Table 3 :

Distribution of Fluorescent antibodies against Lassa, Mopeia, and Mobala viruses.

Location	Total sera tested	Positive sera		
		Lassa V.	Mopeia V.	Mobala V.
Bangassou	22	0	0	0
Botambi	53	0	0	0
Bouar	229	5	1	0
Bouboui	127	0	0	4
Bozo	40	0	0	0
Gomoka	78	0	0	3
Zemio	166	0	0	0

#### 4) Filoviridae :

13% of the CAR samples were found to contain Filoviridae virus specific antibody when screened at a 1 to 16 dilution in an indirect immunofluorescent antibody assay using polyvalent CRELM slides.

All the positive specimens were subsequently titrated on monospecific slides with Ebola, Marburg antigens. The overall antibody prevalence was quite similar to those reported from other countries of the central Africa : Cameroon (1), Zaire (2,3), and Sudan (4,5) ; but higher than that in Gabon (6).

The lowest antibody prevalence was found in the forested Sangha district which is located in the South of the country : 9.9%.

In drier districts such as Ombella-M'Poko, we found a prevalence around 16%.

In the Vakaga district, the prevalence was also around 16%. These findings dispel the idea that human Filovirus infections occur predominantly in moist tropical forest or are associated with particular climatic zones.

Recently, antibodies against Marburg virus have been found in some villages of the district of Vakaga. The specimen found to be positive had been previously collected in children between ten and fifteen years old. In March 1985, we set up a sero survey in Chad in the North of the Vakaga district. In this region, the antibodies against Filoviridae were found to be very high, more than 50%.

We give below in two tables (4,5) the results of 1398 FA tests.

In 1984, a first sero survey showed a high prevalence for EBOLA & MARBURG VIRUS in the CAR:30.8%.

Complete results are listed in table 4.

Table 4:

DATE	ORIGIN	TOTAL	MARBURG	EBOLA (Z)	EBOLA (S)
JUN 84	PAQUA	96	2 / 2.1%	4 / 4.2 %	1 1%
JUN 84	BANGUI	101	0 / 0 %	3 / 3.0 %	0 0%
JAN 85	BALEMBE	31	1 / 3.2%	2 / 6.5 %	1 3.2%
JAN 85	BOUAR	112	1 / 0.9%	9 / 8.0 %	7 6.3%
JAN 85	DIKA	75	5 / 6.7%	9 / 12.0 %	8 10.7%
JAN 85	DONGO BODAM	59	1 / 1.7%	2 / 3.4 %	1 1.7%
JAN 85	NDONGUE	10	0 / 0.0%	0 / 0.0 %	0 0.0%
FEB 85	ZEMIO	140	0 / 0.0%	65 / 46.4 %	0 0.0%
FEB 85	BAMBOUTI	82	0 / 0.0%	50 / 61.0 %	0 0.0%
TOTAL		706	10 / 1.4%	144 / 20.4 %	18 2.5%

In the beginnig of 1985, a second sero survey was undertaken in 3 different areas : SANGHA (Dense forest), OMBELLA MPOKO (Wet savannah), VAKAGA (Pseudo steppe) . Thirteen per cent of these samples (93/692), were found to contain filovirus specific antibodies when screened at a 1/16 dilution, using an indirect immunofluorescent antibody assay. Complete results are listed below, in table 5.

Table 5 : Distribution of FILOVIRUS activity in 3 districts of the CAR (1985):

DISTRICT	VILLAGE	ANTIBODY PREVALENCE (FA)		
		POS.	TOTAL TEST.	%
SANGHA	LIDJOMBO	17	163	10.4%
	BAYANGA	10	97	10.3%
	BABINGO	2	32	6.3%
OMBELLA MPO.	BOZO	15	93	16.1%
VAKAGA	TOUMOU	29	128	22.6%
	AMARDJEDI	3	80	3.8%
	SIKIKEDE	17	99	17.2%
		93	692	13.0%

The overall activity was quite similar to those reported from other parts of central Africa : CAMEROON (4), ZAIRE (5,6), SUDAN (7,8). Nevertheless, this activity seems lower than in GABON (9), but we must note that the studies in that country were undertaken on quite a small number of sera.

Data obtained dispel the idea that human filovirus infection occur essentially in moist tropical forest. In the CAR, and particularly in the VAKAGA district, the antibody rate is about 5 times that found in the arid scrub savannah sample in CAMEROON or in GABON. They merit being compared to those obtained in KENYA .

The VAKAGA findings are particularly surprising since the populations are of the same tribe (They were living in the same village 10 years ago!)

The distribution of end point IFA titers is also interesting but difficult to understand : monospecific EB.sudan are low titered, double positives have similar titer for both EB.Sudan & Zaire though a little bit higher. The possibility of less pathogenic strains is consistent with the somewhat high antibody prevalence as compared to apparent lack of clinical disease. These observations must be compared to those recently obtained in CHAD (Dr.GEORGES : unpublished personal data).

MARBURG results obtained by USAMRIID also seem significant, and there is a need for complementary studies.

#### Discussion:

More detailed study of PHLEBOVIRUS and FILOVIRUS in the CAR is warranted. A number of problems responsible for limitations of previous studies have been overcome. The cooperative program of research set up by USAMRIID and PASTEUR INSTITUTE was successful and allowed us to establish a productive study area.

There are many advantages to studying hemorrhagic fever virus in both OMBELLA MPOKO (RVF), and VAKAGA (EBOLA & MARBURG) districts. Several factors lend credibility to undertaking longitudinal studies in these districts.

#### CONCLUSIONS:

The striking focality of FILOVIRUS activity in the VAKAGA DISTRICT of the CAR represents an exciting finding. It seems interesting to follow the people showing antibodies.

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Proposals for continuing the already successful collaboration between USAMRIID and IPB, to study hemorrhagic fever viruses in the CAR merit being prepared and discussed.

In the VAKAGA district, or in other area with moderate but real filovirus activity, it is important to select and then to follow up a well defined study population. Demographic information must be collected in each village. Fifty to one hundred antibody negative families with presumably similar risk will be chosen to participate in a longitudinal seroepidemiological study. Selected people must be bled at least two or three times each year. Incentive drugs or if necessary and possible, a dispensary will be given to selected villages.

Virus animal interaction merit in being studied in the areas and in the species (peridomestic or wild, or both) which seem to be involved in the biology of FILOVIRUSES.

A research budget including personnel and research support must be accepted before starting this second part of the proposed research program: the global amount could be around 55,000 US Dollars for the first year. A complete evaluation could necessitate at least 2 or 3 years.

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